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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,342	08/01/2001	Shi-Lung Lin	89188.0022	4134

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
01/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/920,342	LIN ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,34-36,38,40-45,55,58-61 and 63-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,34-36,38,40-45,55,58-61 and 63-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/23/2008 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 10/23/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 02/14/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 32, 34-36, 38, 40-45, 55, 58-61 and 63-71 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32, 34-36, 38, 40-45, 55, 58-61 and 63-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 32, 34-36, 38, 40-45, 55, 58-61 and 63-71 are drawn to a method for inhibiting the expression of a target gene through a post-transcriptional gene silencing mechanism in a cell or organism comprising providing a compositions comprising a mRNA-DNA hybrid duplex prior to contacting said cell or organism, wherein the mRNA-cDNA hybrid duplex is used by the cell or organism as a template to generate small gene-silencing effectors inhibiting the expression of said target gene.

Applicant points to support for the claim amendments adding "used by the cell or organism as a template to generate small gene-silencing effectors" on page 1, lines 6-8. A review of page 1 of the instant specification on states that the invention relates to methods of generating mRNA-cDNA hybrids for use in gene silencing and does not provide specific details of said method. The instant specification discloses on page 14 methods for generating mRNA-cDNA hybrids in vitro for gene silencing using primers and promoters in a thermocycling procedure to amplify specific mRNA-cDNA sequences. The specification does not disclose that the mRNA-cDNA hybrid duplex is used specifically by the cell or organism as a template that generates small gene-silencing effectors.

While the instant specification discloses methods of inhibiting target gene expression in vitro using mRNA-cDNA hybrid duplexes wherein these duplexes are generated in vitro before contacting the cell using thermocylcing procedures, this disclosure does not reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of methods of generating small gene silencing effectors using a mRNA-cDNA hybrid duplex template that utilize the cell to make said gene silencing effectors.

If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity, to where such support is to be found.

Therefore, the instant invention is accorded a filing date of 08/01/2001, which is the filing date of the instant application.

Re: Claim Rejections - 35 USC § 112

The rejection of claims 32, 34-36, 38, 40-45, 55, 58-61 and 63-71 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the claim amendments filed 10/23/2008. Response to Applicant's arguments will be addressed below to the extent they apply to the new grounds of rejection.

Claim Rejections - 35 USC § 112

The claim amendments filed 10/23/2008 necessitates the new grounds of rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32, 34-36, 38, 40-45, 55, 58-61 and 63-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting β-cantenin expression *in vivo* in selected organs of chicken embryos using a mRNA-cDNA hybrid duplex, does not reasonably provide enablement for a method of inhibiting expression from any target gene, particularly any cancerous gene, liver or skin, in vivo in any organism using a mRNA-cDNA hybrid duplex and does not provide enablement for inhibiting expression of a target gene using a mRNA-cDNA duplex wherein the duplex is generated in a cell or organism using a mRNA-cDNA template. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims

The claims of the instant invention are drawn to a method for inhibiting target gene expression comprising providing a composition comprising or consisting of an mRNA-cDNA hybrid such that the expression of said gene is inhibited wherein the hybrid is generated in the cell or organism using a mRNA-cDNA hybrid template and wherein said mRNA is in the sense orientation, said cDNA is in the antisense orientation and said mRNA-cDNA hybrid duplex is a complementary region containing more than 500 base pairs. The claims are further limited by requiring that the targeted gene be *in*

vivo, or wherein the gene is pathogenic, viral, mutated, or oncogenic in origin, or wherein said cell is eukaryotic, or is from a vertebrate, which may be a mouse. Newly added claims require the mRNA to be a full-length transcript, an unspliced mRNA transcript or a spliced mRNA transcript.

The specification as filed teaches administration of a mRNA-cDNA hybrid duplex targeted to a gene encoding β-cantenin *in vivo* to chicken embryos, wherein the duplex comprises a fragment of the coding region of β-cantenin and further teach inhibition of β-cantenin expression in selected organs of chicken embryos (see Example 8 of the specification). There is no guidance in the specification as filed that teaches inhibition of expression of any target gene delivered *in vivo* to any organism after administration of a mRNA-cDNA hybrid duplex.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claimed breadth of claims 32, 34-36, 38, 40-45, 55, 58-61 and 63-71 encompass methods of inhibiting any target gene expression in vivo comprising providing a composition comprising small mRNA-cDNA hybrids generated by a template such that the expression of any target gene is inhibited. It must be noted that the claims as now amended recite the mRNA-cDNA hybrid template generates “small gene

silencing effectors". The size range of these small gene silencing effectors is not disclosed in the instant specification and therefore encompasses short interfering RNA capable of post-transcriptional gene silencing. Furthermore, post-transcriptional gene silencing is described in the specification as having the same capabilities as RNAi, which is silencing of gene expression and therefore for purposes of applying art, post-transcriptional gene silencing mechanisms are synonymous with RNAi mechanisms i.e. mechanisms that are capable of silencing gene expression.

Although the specification teaches inhibition of β-cantenin expression in selected organs of chicken embryos after administration of a mRNA-cDNA hybrid duplex, this guidance is not sufficient to resolve the known unpredictability in the art associated with inhibition of gene expression using double stranded nucleic acid and the known unpredictability in the art using RNA-DNA hybrid duplexes.

While the level of one of ordinary skill practicing the invention would be high, the level of predictability is considered to be variable as evidenced by the references cited herein. A thorough review of the patent and non-patent literature indicates that the state of the art for in vivo applications using double stranded duplex was unpredictable, even after the filing of the instant invention, as observed by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586) who states "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by

the vector system, have been problems the gene therapy field has struggled with for over a decade now" (see page 581, last paragraph).

Novina et al. (Nature 2004, Vol.430:161-164) agrees that the "major obstacle to therapeutic gene silencing is the 'delivery problem'- the necessity of introducing short dsRNAs into specific organs" (see page 164, third paragraph). Similarly, Paroo et al. (Trends in Biotechnology 2004, Vol.22(8):390-394) summarizes by stating "[d]eveloping siRNA for efficient gene silencing in vivo is likely to be more challenging and many issues must be addressed before use in animals can become routine. As with any compound, issues of adsorption, distribution, metabolism and excretion are significant obstacles. However, the duplex nature of siRNA introduced an additional layer of complexity. Even with the great progress that has been made, it is not clear whether or not siRNA possesses any advantages relative to traditional antisense oligonucleotides for in vivo experiments or therapeutic development. Crucial pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph).

With respect to using RNA-DNA hybrids to silence gene expression, Parrish et al. teach administration of a RNA-DNA hybrid duplex targeted to a *unc-22* gene of *C. elegans* wherein said RNA-DNA hybrid duplex did not silence gene expression (see Figure 5 page 1081). Parrish et al. teach the loss of *unc-22* expression of *C. elegans* is responsible for a twitching phenotype and *C. elegans* administered a RNA-DNA duplex did not produce the characteristic twitching phenotype associated with loss of *unc-22* expression. Likewise, Tuschl et al. (WO 02/44321) has demonstrated the

unpredictability of inhibition of gene expression using a RNA-DNA hybrid duplex (see Figure 14). Tuschl et al. teach luciferase gene expression was not inhibited in cells after treatment with a RNA-DNA hybrid duplex.

Thus, the instantly claimed invention is not described in the prior art or the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. One of skill in the art could not practice the methods of inhibiting expression from any target gene using a RNA-DNA hybrid duplex without undue, *de novo* trial and error experimentation, because as demonstrated above, it is well known that there is a high level of unpredictability in the art for gene silencing of target genes using a RNA-DNA hybrid duplex. Further, given the teachings of the specification as discussed above, one skilled in the art would not know *a priori* whether introduction of any RNA-DNA duplex by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of any target gene.

To practice the claimed invention, a number of variables would have to be optimized including 1) determining a specific target sequence, 2) targeting the RNA-DNA hybrid to said particular sequence, 3) determining the binding of said RNA-DNA hybrid duplex to said particular nuclei acid sequence such that sufficient inhibition of gene expression occurs. While determination of a particular sequence to target gene and targeting a particular hybrid duplex to said gene may be routine, when taken together to target any gene in any cell such than inhibition of gene expression occurs, the amount of experimentation required becomes such that one of skill in the art could

not practice the claimed invention with a substantial amount of trail and error experimentation.

Applicant argues the teachings of Parrish et al. and Tuschl et al. are not relevant to the present invention because both teach the unpredictability of the use of short RNA-DNA hybrid duplexes for silencing gene expression. Applicant submits that the present invention uses long RNA-DNA hybrid duplex that are larger than 500 base pairs for generation of small gene-silencing effectors and the long RNA-DNA hybrid duplexes are not gene silencing effectors. Applicant's arguments are somewhat confusing and actually support Examiners argument regarding the unpredictability of hybrid duplexes as stated above and in the previous rejection of record. It appears that Applicant is arguing that since the long RNA-DNA hybrid duplexes are not the gene silencing effectors and the short hybrid duplexes of Parrish et al. and Tuschl et al. are used as gene silencing effectors, the findings in each reference would not apply to the instantly claimed invention. The claims as now amended are drawn to a method of inhibiting the expression of a target gene in vivo using small gene silencing effectors which embrace either small hybrid effectors or small double stranded nucleic acid effectors. As stated above, at the time of filing of the instant invention, gene silencing in vivo using double stranded nucleic acids was unpredictable and as shown by Parrish et al. and Tuschl et al., the use of RNA-DNA hybrid duplexes did not efficiently silence gene expression. Therefore, Parrish et al. and Tuschl et al. are clearly relevant to the claimed invention.

Moreover, even if the long RNA-DNA duplexes were used as gene silencing effectors, as stated in the previous Office action, it is well known in the prior art at the time of filing of the instant invention that longer duplexes are cleaved into shorter duplexes once they enter the cell by Dicer and ii is the shorter duplexes are responsible for mediating RNAi. Therefore the findings of Parrish et al. and Tuschl et al. are relevant and provide sufficient efficient in combination with the above factors to find that the instant invention is not enabled for the claimed breadth.

Applicant states that the present invention relates to a post transcriptional gene silencing phenomenon that requires the activity of a RdRp on a DNA-RNA hybrid duplex and this is shown in Figures 4, 6 and Examples 8, 10 and 11 and argues that both Parrish and Tuschl et al. teach the use of Dicer rather than RdRp for generation of siRNAs. At the outset, the claims as recited do not require the use of a RdRp for generation of small gene silencing effectors. While the description of Figure 4 proposes to show a model of PTGS/RNAi/D-RNAi mechanisms, the actual figure does not and only appears to show activities of RdRp and RNase. Figure 6 shows "potential D-RNAi-related RdRp enzymes" and does know show the necessity or methods of using a RdRp on a DNA-RNA duplex. Neither Examples 8, 10 nor 11 show the use of a RdRp to generate small gene silencing effectors.

It appears Applicant is arguing that the present invention requires the use of RdRp and because the small dsRNA taught in Parish et al. and Tuschl et al. require the use of Dicer, they are irrelevant to the predictability or enablement of the claimed invention. As stated above, the present method of inhibiting expression of a target gene

using small gene silencing effectors generated from a mRNA-DNA hybrid template are not limited to the use of a RdRp to generate the small effectors.

Lastly, Applicant argues that the purpose of the enablement requirement is for the patent specification to allow the interested public to make and use the claimed invention, not use a perfected, commercially viable embodiment. This argument is not convincing because as stated above while being enabling for a method of inhibiting β-cantenin expression in vivo in selected organs of chicken embryos using a mRNA-cDNA hybrid duplex, does not reasonably provide enablement for a method of inhibiting expression from any target gene, particularly any cancerous gene, liver or skin, in vivo in any organism using a mRNA-cDNA hybrid duplex and does not provide enablement for inhibiting expression of a target gene using a mRNA-cDNA duplex wherein the duplex is generated in a cell or organism using a mRNA-cDNA template.

Given the unpredictability in the art of using a dsRNA to mediate gene silencing in vivo and the lack of guidance in the instant specification, the breadth of the claimed invention is not enabled.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance.

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/Kimberly Chong/
Examiner
Art Unit 1635